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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,406	02/15/2002	Jeffrey L. Browning	BGNB191CPUSDV	4141

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EXAMINER	
LEE, BETTY L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,406	BROWNING ET AL.	
	Examiner	Art Unit	
	Betty Lee, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54,55,57-60,62,63,66 and 68-87* is/are pending in the application.

4a) Of the above claim(s) *1-53,56,61,64,65 and 67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54,55,57-60,62,63,66 and 68-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed August 22, 2005 is acknowledged. Applicant's election of the species, soluble lymphotoxin-β receptor, without traverse is noted. Claims 1-53, 56, 61, 64 and 65 are canceled. New claims 68-87 are added. Claims 60, 62 and 63 are withdrawn from consideration as directed to non-elected species. Claims 54, 55, 57-59, 66, 68-87 are pending and under examination.

Specification

1. The disclosure is objected to because of the following informalities:

In the disclosure on page 50, line 31 cites Example 11, when it should have been Example 9. In addition on page 51, line 4, there is an underscore after the word "FIG" and no number listed. It is unclear which figure is referred to.

Appropriate correction is required.

Claim Objections

2. Claims 55, 60, 62 and 63 are objected to as containing non-elected subject matter. The claim encompasses nonelected species.

Claim Rejections - 35 USC § 112

3. Claims 54-55, 57, 58, 66, 68-87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting lymphotoxin-β-receptor (LT-β-R) signaling by administering an effective amount of

soluble LT-β-R (SEQ ID NO: 1) or LT-β-R fused to IgG does not reasonably provide enablement for treating a human subject suffering from any autoimmune disorder or any chronic inflammatory disorder, by administering soluble LT-β-R or LT-β-R fused to IgG, any antibody directed against LT-β-R, or any antibody directed against surface LT ligand. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni,

195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986).

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to inhibiting lymphotoxin-beta-receptor (LT-β-R) signaling by administering to a subject with autoimmune disorder or chronic inflammatory disorder, an effective amount of an LT-β-R blocking agent, wherein the LT-β-R blocking agent is selected from a group of consisting of a soluble LT-β-R, an antibody directed against LT-β-R, and an antibody directed against surface LT ligand.

The state of the prior art and the predictability or lack thereof in the art: Browning, *et al* (Cell, 72: 847-856, 1993) teach that the initiation of the immune response involves a complex array of intercellular signals, involving soluble cytokines and cell contact-dependent events (pg 847, col 1). Browning, *et al* further teach that tumor necrosis factor (TNF) and lymphotoxin (LT) are related cytokines whose "roles in

the immune system are somewhat of an enigma since *in vivo* experiments suggest critical functions, yet the corresponding *in vitro* work has not led to a very clear picture of their place in T and B cell regulation" (pg 847, col 1, paragraph 1). Therefore, it is unpredictable whether any LT-β-R blocking agent is enabled for use as a method to treat autoimmune disorder or chronic inflammatory disorder as encompassed by the claimed invention.

The amount of direction or guidance present and the presence or absence of working examples: The specification provides limited guidance with regard to how to make and use therapeutically effective LT-β-R blocking agent. Examples 3-7 (pg 43-47) disclose the effects of LT-β-R blocking agents *in vitro*, while examples 9 and 10 disclose animal models of Inflammatory Bowel Disease (IBD) and example 11 disclose an animal model of Delayed Type Hypersensitivity (DTH). Although the specification discloses examples of IBD and DTH, the Applicant is not enabled to treat all autoimmune disorders which include psoriasis, rheumatoid arthritis, diabetes mellitus, multiple sclerosis, sympathetic opthalmia and uveitis. Neither is the Applicant enabled to treat all chronic inflammatory disorders which include IBD, Crohn's disease and ulcerative colitis. There are no working examples of therapeutic efficacy of using soluble LT-β-R, an antibody directed against LT-β-R, and an antibody directed against surface LT ligand to treat psoriasis, rheumatoid arthritis, diabetes mellitus, multiple sclerosis, sympathetic opthalmia, uveitis, Crohn's disease and ulcerative colitis.

In addition, the claimed invention is drawn to " a soluble lymphotoxin–β receptor, an antibody directed against LT-β-R, and an antibody directed against surface LT

ligand". The specification discloses a soluble lymphotoxin–β receptor comprising SEQ ID NO:1, an antibody directed against human LT-β-R (BDA8 mAb), mouse LT-β-R-Fc and human LT-β-R-Fc. The specification discloses surface LT ligand comprising lymphotoxin-β (pg 13, lines 26-38 and pg 14, lines 1-21). Therefore, the Applicant is not enabled for ANY soluble lymphotoxin–β receptor, ANY antibody directed against LT-β-R, ANY antibody directed against surface LT ligand and ANY surface LT ligand.

The breadth of the claims and the quantity of experimentation needed: The claims are directed to a broad spectrum of LT-β-R blocking agents that are not supported in the specification. In addition, the claims are also directed to treating any autoimmune disease and chronic inflammatory disorder with LT-β-R blocking agents, which are not supported in the specification. Given the unpredictability of treating autoimmune or inflammatory diseases, it would require undue experimentation for a person of skill in the art to be able to use the invention as described.

4. Claims 54, 55, 57-60, 62, 63, 66, 68-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description"

Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is *whatever is now claimed* (see page 1117).

A review of the language of the claim indicates that these claims are drawn to four genera, i.e., 1) soluble lymphotoxin–β receptors, 2) antibodies directed against LT-β-R, 3) antibodies directed against surface LT ligand and 4) surface LT ligands. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states An adequate written description of a DNA ... requires a precise definition, such as by structure,

formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention.

There are five species of the claimed genera disclosed that is within the scope of the claimed genera, *i.e.* 1) a soluble lymphotoxin–β receptor comprising SEQ ID NO:1, 2) an antibody directed against human LT-β-R (BDA8 mAb), 3) mouse LT-β-R-Fc 4) human LT-β-R-Fc and 5) surface LT ligand comprising lymphotoxin-β. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. There is substantial variability among the species.

One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genera of which comprise1) a soluble lymphotoxin–β receptors, 2) antibodies directed against LT-β-R, 3) antibodies directed against surface LT ligand and 4) surface LT ligands. The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 59, 63 and 73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59 cites 'the LT-β-R blocking agent comprises a soluble LT-b-R further comprising a human immunoglobulin Fc domain.' It is unclear because of the sentence syntax whether the blocking agent or the soluble LT-B-R further comprises a human IgG Fc domain.

Claim 63 cites a 'subunit' of the LT ligand. This term is indefinite because it is unclear which subunit is encompassed by the phrase.

Claim 73 cites 'a functional sequence of amino acids'. It is unclear what is meant by a 'functional sequence'.

Thus, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 54, 55, 57-59, 66, 68-74, 76, 77, 78, 81, 83-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crowe, *et al* (Science 264:707-710, 1994) in view of Mohler, *et al* (J. Immunol. 151:1548-1561, 1993).

The claimed invention is drawn to a method for inhibiting lymphotoxin-beta-receptor (LT-β-R) signaling comprising administering to the subject an effective amount of soluble LT-β-R (SEQ ID NO: 1) fused to human immunoglobulin Fc domain for in vivo administration.

Crowe, *et al* teach that lymphotoxin-β-receptor (SEQ ID NO: 1), a member of the TNF family, has sequence similarity to TNF receptor (pg 708, col 1). Crowe, *et al* teach that the LT-β-R/Fc fusion protein binds to the major cell surface LT complex (pg 708, col 3) and suggests a role for the LT-β-R in immune development (pg 709, col 2). Crowe, *et al* teach that the expression of LT complexes by activated lymphocytes suggests a function as positive or negative regulators in inflammatory and immune responses (pg 709, col 1). Crowe, *et al* do not teach the administration of soluble LT-β-R fused to IgG for inhibiting the lymphotoxin-beta-receptor.

Mohler, *et al* teach that recombinant soluble receptors administered *in vivo* show potential to inhibit immune and inflammatory responses by acting as antagonists of cytokine activity (pg 1549, col 1). Mohler, *et al* teach the construction of human monomeric and dimeric Fc fusion proteins of TNF receptor (pg 1549, col 1, pg 1550, Fig 1) and suggest that the soluble TNFR:Fc molecule may be a useful therapeutic agent for sepsis and other inflammatory diseases (pg 1559, col 1). In addition, Mohler, *et al* teach that dimeric Fc fusion proteins have superior TNF inhibitory activity (pg 1549,

col1). Mohler, *et al* teach the intravenous administration of soluble TNFR:Fc in mice (pg 1551, col 1) showing beneficial results of protection from the lethal effects of LPS injections. Although neither Crowe *et al.* nor Mohler *et al.* teach administration of the fusion protein at specific doses, it is within the purvue of one of ordinary skill in the art to determine the appropriate dosage regimen for therapeutics.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a fusion protein comprising the soluble LT-β-R (SEQ ID NO: 1) taught by Crowe, *et al* and fused to human immunoglobulin Fc domain, as taught by Mohler, *et al.* The person of ordinary skill in the art would have been motivated to construct the fusion protein because Mohler, *et al* teach that fusion proteins are more potent as competitive inhibitors than monomeric soluble receptors. The person of ordinary skill in the art would have been motivated to administer the soluble LT-β-R complex for treatment in chronic inflammatory and autoimmune diseases because LT-β-R as part of the TNF family, plays a role in inflammatory and immune responses.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Betty Lee, Ph.D. whose telephone number is (571) 272-8152. The examiner can normally be reached on M-F 9 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BLL

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